Environmental Occupational, and Genetic Risk Factors for α-1 Antitrypsin Deficiency

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α-1 Antitrypsin (AAT) deficiency is an inherited genetic disorder currently diagnosed in approximately 5,000 people in the United States. Although some individuals with AAT deficiency are asymptomatic, the condition often leads to deterioration of lung function in adults and is associated with emphysema, asthma, chronic obstructive pulmonary disease, and other respiratory diseases. In children, AAT deficiency can result in severe liver disease, including fatal cirrhosis in newborn infants. Although much is known about the clinical pathology of AAT deficiency, researchers are just beginning to characterize environmental, occupational, and genetic modifiers affecting the onset and progression of diseases related to AAT deficiency. On 19 August 2002, a group of basic scientists, clinicians, environmental health researchers, and public interest groups gathered at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, to discuss ongoing research on these topics. The goals of this workshop were to *a*) assess the present state of knowledge regarding environmental and occupational risk factors contributing to AAT deficiency morbidity and mortality, *b*) define future research needs in this area, and *c*) explore collaborative opportunities to advance understanding of risk factors affecting the progression of AAT deficiency–related disease. Participants agreed that new research initiatives in these areas represent an opportunity to benefit both basic science, through enhanced understanding of gene–environment interaction, and the AAT deficiency patient community, through innovative new approaches to disease management and treatment. *Key words:* **alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, emphysema, environmental risk factors, gene–environment interactions, genetic testing, liver disease, neutrophil elastase, occupational health.** *Environ Health Perspect* **111:1749–1752 (2003). doi:10.1289/ehp.6325 available via *http://dx.doi.org/* [Online 23 July 2003]**

α-1 Antitrypsin (AAT) deficiency is an inherited genetic disorder associated with lung and liver disease. It is a rare form of panniculitis and is related to a high risk for development of jaundice in infants, liver disease in children and adults, and pulmonary emphysema in adults (for review, see McBean et al. 2003). AAT is coded by a single gene on the long arm of chromosome 14. Codominant allelic expression results in a hereditary deficiency of AAT, a glycoprotein produced mainly in the liver. Although there are a number of naturally occurring variants of AAT, the two most common deficiency variants, S and Z, are the result of point mutations in the *AAT* gene. In these variants, the migration of the protein is retarded. The S variant (*Glu264Val*) can result in a 40% deficit in plasma protein levels. However, it has yet to be linked to any significant clinical disorder. The Z variant (*Glu342Lys*) results in severe plasma deficiency and the manifestation of severe progressive clinical disease. The major function of AAT is to protect the lung against the enzyme neutrophil elastase. In the normal lung, AAT exists in balance with neutrophil elastase, a proteolytic enzyme that digests damaged or aging cells and microbes. The disruption of this balance as occurs with AAT deficiency reduces or eliminates the inhibitory antiprotease action of AAT, and neutrophil elastase activity goes unchecked. When unregulated, neutrophil elastase can attack sensitive lung tissue, resulting in airway hyperresponsiveness (Malerba et al. 2003), particularly when the lung is challenged by stressors that increase levels of neutrophil elastase in the respiratory system, such as tobacco smoke (Hutchison et al. 2002), environmental irritants, and infection. Over time, the resulting tissue damage can result in deterioration of lung function, leading to emphysema, chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, and asthma (Eden et al. 1997, 2003; Lee et al. 2002; Parfrey et al. 2003; Piitulainen and Sveger 2002).

Current treatment for AAT deficiency often involves augmentation of the AAT protein itself via intravenous infusion of Prolastin, which is purified AAT derived from pooled human plasma (Sandhaus 1993, 2001; Stoller et al. 2003). Typically indicated in patients with AAT deficiency–related emphysema, this correction of the biochemical imbalance in the respiratory system can help slow or halt the progression of deterioration in lung function. Currently, few data exist suggesting further development of gene therapy as a mechanism to combat this disease (Brigham et al. 2000; Dasi et al. 2001; Flotte 2002; Metz et al. 2002; Song et al. 2001; Stecenko and Brigham 2003; Stoll et al. 2001). However, at this time, treatment modalities for AAT deficiency–related respiratory disorders, beyond AAT augmentation therapy, often include behavior and lifestyle changes (e.g., smoking cessation, avoidance of environmental irritants and infections, exercise) and other therapies associated with the treatment of obstructive lung disease, including bronchodilators, corticosteroids, and supplemental oxygen. In severe cases, lung volume reduction surgery and lung transplantation have also been successfully employed.

Although the mechanism at work is not yet fully understood, AAT deficiency also leads to liver disease in many patients, including hepatitis, cirrhosis, and liver failure, particularly in individuals with the homozygous *ZZ* (*PiZ*) AAT allele. In *PiZ* individuals, the low circulating levels of AAT appear to be due to the accumulation of abnormally folded AAT protein within the hepatocytes. Approximately 12–15% of Alphas (persons suffering from AAT deficiency) experience liver disease. Approximately 10% of newborns with the *PiZ* allele have liver disease that leads to fatal childhood cirrhosis (Alpha-1 Association 2002). Persons with the null-null allele, who produce no AAT at all, do not appear to experience liver disease, which would support the hypothesis that the accumulation of abnormal AAT in the endoplasmic reticulum of hepatocytes may be the driving pathologic factor in AAT deficiency–related liver disease. Prolastin is not used to treat AAT deficiency–related liver disease. The only available treatment for individuals with end-stage liver disease resulting from AAT deficiency is liver transplantation, which has been successful in some patients with severe AAT deficiency–related liver disease. In addition to clinical pathologies associated with lung and liver disease, AAT deficiency has also been associated with necrotizing panniculitis and vasculitis, particularly Wegener's granulomatosis (Lonardo et al. 2002).

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The authors declare they have no conflict of interest.

Received 10 March 2003; accepted 23 July 2003.

Many believe that this disease often goes undetected or misdiagnosed, especially in the early stages. To address many of the concerns of AAT deficiency patients and to raise the awareness of the disease with the public, researchers, and funding agencies, the Alpha-1 Foundation was founded as a patient and research advocacy group, based in Miami, Florida. The foundation estimates that roughly 5,000 cases of AAT deficiency have been diagnosed in the United States (Alpha-1 Foundation 2002) and is actively pursuing improvements in this area, including a targeted detection program in Florida with the goal of testing every patient in the state with COPD or unexplained liver disease, and every adult and adolescent with chronic asthma. This foundation, in collaboration with academic researchers and clinicians and with the National Institute of Environmental Health Sciences (NIEHS), organized a workshop that would bring together these various interested parties to discuss the current knowledge base and to raise questions specifically with regard to the contribution of environmental factors in the manifestation and progression of the disease.

Workshop Summary

On 19 August 2002, a multidisciplinary group of interested parties gathered at the NIEHS in Research Triangle Park, North Carolina, to exchange information and ideas pertaining to the investigation of environmental, occupational, and genetic risk factors that may contribute to the onset and progression of AAT deficiency–related disease. The workshop, titled "Environmental, Occupational, and Genetic Risk Factors for Alpha-1 Antitrypsin Deficiency," was sponsored by the NIEHS, the Office of Rare Disease Research of the National Institutes of Health (Bethesda, MD), the Alpha-1 Foundation, and AlphaNet, a not-for-profit health management company serving the AAT community. The overarching goals of the workshop were to *a*) assess the present state of knowledge regarding environmental and occupational risk factors contributing to AAT deficiency morbidity and mortality, *b*) define future research needs in this area, and *c*) explore collaborative opportunities to advance understanding of risk factors affecting the progression of AAT deficiency–related disease.

John Walsh, current president of the Alpha-1 Foundation and one of several participants who were Alphas themselves, set the tone for the day's deliberations in his opening remarks. He stressed the importance of expanding research efforts on AAT deficiency and developing new therapies or preventive interventions. His hope was that new therapeutic options would emerge from research initiatives on AAT deficiency designed to clarify the role of environmental risk factors in modulating the onset and progression of the disease:

> The importance of this workshop to our community is significant. Right now in our community, we have one therapy, and it's in critical short supply. We think if we can focus on. . . environmental risk factors, we're going to be able to positively impact the course of this devastating chronic illness. We look at this as a preventative form of medicine, and maybe we can stop the progression of the disease completely, which would be great. . . . At least maybe we can slow down the progression.

The first session of the conference, moderated by Richard R. Sharp of the NIEHS, provided an overview of the natural history of AAT deficiency, diagnosis, and treatment options. Robert Sandhaus, Clinical Director and Executive Vice President of the Alpha-1 Foundation, summarized significant developments in the history of AAT lung and liver disease (Table 1). After this history, Sandhaus discussed diagnostic criteria and common therapeutic strategies (Sandhaus 2002). James Donohue, a pulmonologist at the University of North Carolina at Chapel Hill and the second speaker in the session (Donohue 2002), presented a clinician's point of view about diagnostic challenges (Table 2), the management of persons with AAT deficiency, and the use of augmentation therapy (Schluchter et al. 2000). James Stocks of the University of Texas Health Center at Tyler concluded the session by describing ongoing efforts to improve AAT augmentation therapy and expand the scope of therapeutic options available to persons with AAT deficiency (Stocks 2002).

With the workshop's attention focused on new research initiatives, the second session, moderated by G. Jean Harry of the NIEHS, centered on the current state of research regarding the treatment of AAT deficiency. Bruce Trapnell of the University of Cincinnati and the Alpha-1 Foundation presented an overview of the foundation's research program (Trapnell 2002). After this presentation, Charlie Strange of the Medical University of South Carolina provided more details (Strange 2002b) about the Alpha-1 Foundation's Research Registry (http://www.alpha1registry.org), which has served as an important resource for the development of AAT deficiency–related research. The registry was initiated in 1996 and within the first year had only 100 patients participating. This increased to approximately 500 patients by 1998, and by 2000 the registry contained 900 patients. During the years 2001–2002, an additional 1,000 or so patients were registered, bringing the total to 2,062 participants. Also during this session, Frederick de Serres, a former NIEHS scientist who has AAT deficiency, outlined his ongoing research on the worldwide distribution of alleles associated with AAT deficiency (de Serres 2002a). By analyzing data from more than 400 control cohorts in peer-reviewed studies in 60 countries covering 11 major geographic regions, de Serres has uncovered evidence suggesting a much more widespread distribution of the two most common deficiency alleles, PiS and PiZ (de Serres 2002b; de Serres et al. 2003)

The third session of the conference reviewed research on environmental, occupational, and genetic risk factors associated with AAT deficiency, particularly factors affecting the development of COPD and other lung diseases. Edwin Silverman of Harvard University described his and other investigators' work on the genetics of COPD in AAT-deficient and nondeficient subjects (Silverman 2002). In addition to his ongoing research into the genetics of early-onset COPD, which may shed light on some aspects of AAT deficiency, he and collaborators at eight clinical centers are presently in the early stages of a study seeking to identify genetic modifiers of AAT deficiency. The second speaker in the session, Sverre Vedal of the National Jewish Medical and Research Center, explored various methodologies used in studies conducted on ambient air pollution and occupational exposures believed to be related to COPD, with an emphasis on how various study designs could be used in similar investigations of environmental risk factors for AAT deficiency (Vedal 2002). Building upon that foundation, Annyce

Table 1. Significant events in the history of AAT deficiency.

< 1963 Familial emphysema initially described in Sweden
1963 Laurell and Eriksson describe association between familial emphysema and deficiency of α_1
1964 Gross describes animal model of emphysema caused by intratracheally instilled papain
1965–1967 Appreciation of role of elastase
1965–1967 Fagerhol describes allelic variation of AAT
1967 Janoff describes neutrophil elastase
1969 Sharp describes association with neonatal cirrhosis
1971–1975 Inhibition of neutrophil elastase by AAT; role of oxidants
1980s α_1 Augmentation therapy; epidemiology of α_1 explored

Specific references in the history of AAT deficiency are cited by Sandhaus (1993, 2001, 2002).

Table 2. Clinical symptoms suggesting AAT deficiency.

COPD
Asthma
Family history of AAT deficiency
Unexplained chronic liver disease
Bronchiectasis
Panniculitis
Unexplained vasculitis, particularly of Wegener's granulomatosis type

If these conditions are seen in nonsmokers of any age, or if COPD occurs at age 30–55 in smokers, the likelihood of AAT deficiency is considerable. Adapted from Donohue (2002).

Mayer of National Jewish Medical and Research Center presented an overview of existing research into environmental and occupational exposures and AAT deficiency (Mayer 2002), arguing that although the literature contains several important studies to date, more research is needed (Mayer and Newman 2001; Mayer et al. 2000). The session concluded with University of Florida bioethicist Ray Moseley's exploration of the complex ethical and legal issues involved in identifying genetically susceptible populations, particularly with respect to informed consent and the testing of children and young adults for genetic conditions (Moseley 2002).

The workshop culminated with a panel discussion about future research on environmental and occupational risk factors associated with AAT deficiency. The goals of this concluding session, moderated by Lee Newman of National Jewish Medical and Research Center, were to identify critical unanswered research questions and to explore strategies for bringing environmental health researchers, the patient community, and funding agencies together in efforts to answer some of those questions.

Recommendations

Participants agreed that the natural history of AAT deficiency is still not well understood. As Sandhaus expressed it, "Clearly, … the epidemiology of Alpha-1 and [its] natural history is one of the areas of great deficit that's been identified all along, and it still is in need of a great deal of further research." For example, there is a need to identify early biomarkers of AAT deficiency, including markers that might help to explain why some Alphas remain asymptomatic whereas others develop emphysema and/or liver disease. Similarly, although the Z allele appears necessary for the development of AAT deficiency–related emphysema, it is not sufficient in and of itself to account for the onset of disease. Trapnell and others suggested that it is important to look for other genetic and/or environmental factors at work that may contribute to the differential manifestation of various adverse effects within the AAT patient population.

Several participants stressed the idea that identification of early biomarkers, additional genetic factors, and environmental contributions would directly serve the AAT community. Such information would allow for earlier preventive interventions, such as lifestyle adjustments, career planning, and avoidance of harmful environmental exposures. A more precise definition of risk factors might also allow for targeted screening and detection of persons at risk.

In addition, there was consensus that research exploring the role of environmental factors in the initiation, manifestation, and progression of clinical symptoms in people with AAT deficiency represents a clear opportunity to advance basic research and simultaneously provide benefit to patients. The AAT deficiency patient population clearly represents a subpopulation susceptible to numerous airway stimulants as well as other inflammatory agents or processes. The detailed examination of this population will contribute to the clinical population with regard to diagnosis, prevention, and maintenance of the disease as well as providing information regarding factors and agents that may produce adverse effects in various susceptible subpopulations. Just as the identification of an association between plasma deficiency of AAT and emphysema led to the proteinase–antiproteinase hypothesis of lung disease, any additional understanding of the role of aberrant protein polymerization in AAT deficiency could contribute to the development of novel therapeutic strategies (Carrell and Lomas 2002; Devlin et al. 2001; Lomas and Mahadeva 2002; Perlmutter 2002). de Serres, speaking from the dual perspectives of an Alpha and a scientist, expressed this convergence of interests:

> All people are not created equal, and some of us are uniquely susceptible.… I think it's a matter of developing the right approaches in the laboratory to see if there are ways of evaluating quickly the effect of either environmental exposure to chemicals or to particulates, rather than waiting long-term for us to develop asthma, bronchiectasis, and the variety of other problems that plague most of us.

Participants also agreed that the Alpha-1 Foundation's Research Registry (http://www.alpha1registry.org; Stoller et al. 2000; Strange 2002a) is a major asset for researchers interested in examining gene–environment interactions. Many individuals in the registry are highly sensitive to environmental exposures, and their AAT deficiency status is well characterized, making this a unique research resource. Several speakers did express concerns about inherent biases in the registry, however, that could limit its utility as a research tool. For example, the registry may be biased toward individuals of higher socioeconomic status, who are likely to live and work in less harmful environments, potentially biasing data in the direction of the null hypothesis when examining the effects of environmental exposures. Additionally, because persons in the registry have been identified largely as a result of health problems indicative of advanced disease, participants in the registry are likely to be less healthy than the larger population of Alphas, which could be problematic in assessing the natural history of AAT deficiency. Although participants acknowledged these limitations, many felt the registry could continue to play an important role in future research and that innovative study designs might be developed for examining environmental and occupational risk factors in the context of the registry.

In addition to these efforts, a number of participants supported the development of large cohort studies designed to overcome the ascertainment biases of collections such as the Alpha-1 Registry (Stoller et al. 2000; Strange 2002a). Such cohort studies could shed light on the natural history of AAT deficiency and suggest key environmental and genetic factors involved in the progression of AAT deficiency–related disease. Silverman drew attention to a study of Swedish newborns with AAT deficiency (Sveger 1978; Sveger and Eriksson 1995; Sveger and Thelin 2000; Sveger et al. 1999). In that study, 200,000 Swedish infants were screened for AAT deficiency in the early 1970s, with nearly 200 Alphas identified (Laurell and Sveger 1975; Sveger 1978). These persons are periodically reexamined to track the impact of AAT deficiency on their health. Because the Swedish cohort is still years away from yielding definitive answers to many questions about the natural history of AAT deficiency, however, Silverman and others suggested that it may be appropriate to undertake large population screening programs to acquire a non-ascertainment-biased set of AAT-deficient subjects. This suggestion was embraced by John Walsh of the Alpha-1 Foundation, who asked:

> Do we wait thirty years for the Swedish newborns study to be done, or do we take that bold step and spend whatever amount of money it's going to take to do an appropriate population study to ascertain what the real prevalence or incidence is? … If the answer is, "We'd better do that," then let's do it and let's not wait. Thirty years is not acceptable to anybody that I know that has Alpha-1.

AAT deficiency is clearly more prevalent than previously thought, and the information exchanged among the participants at this workshop showed that investigation of the influence of environmental and occupational risk factors on the onset and exacerbation of AAT deficiency–related disease will be an important new direction in research associated with this often fatal condition. New information in that arena will complement simultaneous progress made in the understanding of genetic susceptibility to AAT deficiency, and of the disease process itself, both of which are in critical need of additional research. At the same time, research attention must be paid to the often complex ethical, legal, and social issues raised by genetic testing, gene–environment interactions, and the identification of environmental and occupational risk factors, as they affect this uniquely susceptible population. Innovative and imaginative research initiatives resulting from collaborations among the various interested groups hold the promise of one day providing new answers to the many open questions remaining about AAT deficiency, and contributing to new management strategies, improved therapies, and an eventual cure.

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